REMARKS

Examiner has objected to several informalities within the specification. Applicant's acknowledge those informalities and have amended the specification with the appropriate corrections as requested by examiner to place the specification in a condition for allowance. Claim 6 is canceled at the request of Applicant. Claim 8 has been revised to more accurately define the function of combining the weighted crystallographic phases from a model structure with phase probability distributions from Claim 1 step (g) to form a composite set of structure factors that include phase probability information from both the model and from the expected features of the electron density map.

Examiner has rejected Claims 1-8, now pending in the application, under 35 U.S.C. 102(b) as being clearly anticipated by Murshudov et al. Applicants respectfully traverse these rejections.

Claim 1:

Applicant's agree that Murshudov et al. does teach steps a, b, and c of Applicant's Claim 1, which describes the standard crystallographic procedures of obtaining structure factors, calculating phases, and drawing an electron density map. Applicant's also agree that Murshudov et al. does teach steps h, i, and j of Claim 1, which describes the repetitive application of the methods in steps a,b,c,d,e,f,g.

However, Murshudov et al. does not teach steps d, e, f, and g of Applicant's Claim 1, which describes the analysis of an electron density map to obtain expectations about the electron density distributions in the map, comparisons of the current map with expectations, estimating how changes in structure factors will affect this comparison, and establishing phase probability distributions from these comparisons.

A key element of steps d, e, f, and g of Applicant's Claim 1 is the calculation, for each point in the electron density map, of a probability distribution for expected electron density. These probability distributions of expected electron density are a way of

capturing the information that is obtained by (1) examining a noisy map and identifying the presence of features in that map (e.g., the location of the solvent region, or the location of a helix), and (2) inferring that the true map contains idealized versions of the features found in the noisy map, and (3) using the expectation that these idealized features are present to derive a new estimate of the electron density at each point in the true map, and an estimate of the uncertainty in the estimate of the electron density. The estimates of electron density and corresponding uncertainty (described as a probability distribution of electron density) are the fundamental information that is then used to calculate phase probabilities. Murshudov et al. does not anticipate the use of probability distributions for electron density.

It is important to note that both the estimate of electron density and corresponding uncertainty vary from point to point in the map. The specification that certain parts of the map are known accurately and other parts are not is not taught by Murshudov et al. and makes an essential contribution to the procedure taught in the present invention. Also important to note, the features that are identified in the map are normally not the presence of the atoms in the current atomic model of the macromolecule, but rather a different set of features (such as the flatness of the solvent region) that yield independent information. It is the use of this independent information in the present invention that makes the removal of bias from the model of the macromolecule particularly effective. Such a use of independent information and avoidance of use of the atomic model in estimating new phases is not taught by Murshudov et al.

Claims 2, 3, 4 and 5:

Each of these claims describes a class of features of an electron density map that can be used in Claim 1, steps d,e,f, and g to obtain and use a probability distribution for electron density. Murshudov et al. does teach the existence of each of these features of a map, however, Murshudov et al. does not teach their use in obtaining a probability distribution for electron density. Further, as Claim 1 is now a novel allowable claim these dependent claims are now allowable as well.

Claim 7:

Murshudov et al. teaches the use of maximum-likelihood functions and FFT methods for calculation of derivatives for refinement of macromolecular structures, but does not teach their use in estimating phase probabilities from probability distributions for electron density. Further, as Claim 1 is now a novel allowable claim this dependent claim is now allowable as well.

Claim 8:

Murshudov et al. teaches the use of a model structure having similarities to the crystal structure being examined and the use of weighting factors to reduce model bias, but does not teach the use of either in the method of Claim 1. Stated another way, as Claim 1 is now a novel allowable claim this dependent claim is now allowable as well.

Therefore, the Examiner is requested to allow Claims 1-5, and 7-8, and to pass this case to issue.

Applicant's attorney would be pleased to further discuss this matter by telephone with the Examiner if the Examiner concludes such a discussion would assist in moving this case to issue.

No new matter has been added as a result of this response.

Respectfully submitted,

Signature of Attorney

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